

Study Protocol

Cessation in Non-Daily Smokers: a RCT of NRT with Ecological Momentary Assessment (QUITS)

NCT Protocol #: NCT02168855

Local IRB #: PRO12070152

Protocol Date: 06/02/2016



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Research Protocol Abstract:

US smoking patterns are changing dramatically: non-daily, or intermittent smokers (ITS) now comprise a quarter or more of all adult smokers in the US and appear to be rising dramatically, both in the US and in Europe. Despite their non-daily exposure to cigarettes, they suffer serious smoking-related morbidity and mortality. While ITS' smoking does not seem to be associated with nicotine regulation processes traditionally viewed as inherent to dependence, we and others have shown that ITS have trouble quitting: Although ITS made more efforts to quit smoking than regular daily smokers (DS), they had failure rates of up to 79%- almost as high as those of DS, and also sought out quit aids, including medications. The high failure rates were not due to residual nicotine dependence from a history of past daily smoking – ITS who had never smoked daily had the lowest quit rates⁵. Our studies of ITS also raise fundamental questions about the role of nicotine in ITS smoking: We have shown that ITS take in and clear nicotine in the same way as DS, but the role of nicotine in ITS smoking and cessation is not clear. There have been no studies of pharmacological treatment in this population. We propose a randomized trial to test the role of acute as-needed nicotine medication (nicotine gum) to aid cessation among ITS. Testing nicotine medication in ITS addresses two questions: a clinical treatment efficacy question and a more basic question of whether nicotine plays a crucial role in motivating ITS' smoking. Theorists have recently proposed that ITS are nicotine-dependent, much as DS are, but simply differ in the frequency with which they need nicotine and experience craving. This theory predicts that ITS will suffer craving and withdrawal, but with late onset, in contrast to the pattern observed among daily smokers, where craving and withdrawal diminish over time. We have, in fact, observed some signs of nicotine dependence in our recent study of ITS. On the other hand, the data show that ITS' smoking is driven by stimulus control – exposure to specific, often idiosyncratic, stimuli and situations that prompt smoking (e.g., social venues, stress). This suggests that re-exposure to such stimuli may play a large role in relapse among ITS, and that ITS may benefit from acute doses of nicotine in those situations. Oral nicotine medication such as nicotine gum, which we have shown to reduce acute cue-provoked craving in daily smokers, is ideally suited to provide such acute 'rescue' treatment. Our aim is to study the effect of as-needed oral Nicotine Replacement Therapy (NRT) – 2 mg nicotine gum – for smoking cessation in ITS, and to study the process of relapse in ITS, using Ecological Momentary Assessment (EMA). Reviews of ITS have called for research on ITS' relapse process, and for evaluation of cessation methods, including medications, among ITS. Yet, no study to date has examined the cessation or relapse process in ITS, or tested the use of nicotine medications in this population.

We propose a double-blind, randomized, placebo-controlled trial of oral NRT for smoking cessation in ITS. 600 ITS who are interested in quitting will be recruited through multiple channels. Enrollees will be randomized 1:1 to active 2 mg nicotine gum or an inert control gum. Participants will attend 6 sessions with brief behavioral support, with a planned quit day at week 2. Short and long term abstinence will be assessed and

biochemically validated. EMA data collection includes two weeks of baseline data on ad lib smoking patterns and 6 weeks of post-quit data, using methods we successfully fielded in our previous research. This will capture data on craving, withdrawal, and relapse among ITS, and relate relapse contexts to baseline smoking patterns. We propose a study specifically focused on ITS, rather than a comparison to DS, as the need is to understand cessation and the role of nicotine among ITS per se. Comparisons with DS (including light daily smokers) may be more informative at a later stage.

Section 1 - Objective, Aims, Background and Significance

The overall purpose of this research study:

The purpose of this study is to examine the efficacy of as-needed oral Nicotine Replacement Therapy (NRT) – 2 mg nicotine gum – for smoking cessation in non-daily, or intermittent, smokers (ITS), and to study the process of relapse in ITS, using Ecological Momentary Assessment (EMA).

Specific Aims:

Aim 1: Test whether nicotine gum can help ITS quit smoking, in order to:

Clinically assess the efficacy of acute nicotine replacement therapy (NRT) in improving quit rates in ITS.

H1: ITS randomized to oral NRT will have higher rates of 6 month abstinence compared to ITS using placebo.

Conceptually, assess the role of nicotine in ITS' difficulty quitting and thus in their smoking. If NRT is effective in helping ITS quit, this will demonstrate that ITS' smoking is motivated by nicotine-seeking.

Aim 2: Use EMA methods to capture quit and relapse process in ITS, in order to determine:

Sub-aim 1: Whether ITS suffer increasing craving and withdrawal-like distress after prolonged and variable periods of abstinence.

H2-1: ITS will suffer resurgence of craving and withdrawal after an individual-specific interval of abstinence.

Sub-aim 2: Whether ITS' temptations and lapses occur specifically in situations previously associated with their individual smoking patterns, as implied by a stimulus control theory of ITS' smoking and relapse.

H2-2: ITS' temptations and lapses will be predictable based on their baseline smoking patterns.

Background:

Over 25% of smokers are ITS, and their proportions are rising. Smoking patterns are changing dramatically in the US and elsewhere. The proportion of smokers who are non-daily smokers (intermittent smokers – ITS) is high, and rising steeply. Once considered rare anomalies, ITS now constitute 25-33% of smokers, and this proportion rose by 40% from 1996 to 2001. Using national data, our team has shown that, despite their intermittent smoking patterns, ITS have trouble quitting, and have failure rates (79%) almost as high as those of daily

smokers (DS; 87%). Moreover, about a fifth of ITS sought out and used pharmacological treatment (primarily NRT) in their quit attempt, despite the fact that treatment is usually sought only by those who feel unable to quit on their own. ITS' need for and desire for treatment is reinforced by a study of workplace smoking cessation treatment, where ITS were just as likely as DS to take up an offer of counseling. Thus, ITS are an increasingly prevalent yet poorly understood segment of the smoking population – and one that has been overlooked in interventions.

Data on ITS smoking patterns from our recent study of ITS suggest why ITS might benefit from pharmacological treatment. ITS take in as much nicotine per cigarette as DS, and metabolize it just as quickly, so their smoking may well be motivated by nicotine-seeking. It is not clear what effects of nicotine ITS may be seeking in such situations, but situation-specific drug-seeking is not uncommon. Moreover, our data show that ITS have some degree of tobacco dependence, albeit at much lower levels than DS. A group of prominent theorists have recently suggested that ITS are nicotine-dependent in the same way as DS, and differ from DS only in that their periodic need for nicotine occurs less frequently, not requiring daily intake. An alternative account suggests that ITS' dependence and difficulty quitting is due to strong and persistent stimulus associations with smoking. Our data show that ITS' smoking is strongly stimulus-bound, occurring in response to particular cues, which may act as discriminative stimuli, signaling reinforcement from nicotine. Repeated pairing of smoking and nicotine with such stimuli may lead to strong learned associations, and our data show that such stimuli come to evoke strong cravings. These effects can be persistent and compelling, even after smoking has ceased. These models may help explain the challenges ITS may face when quitting, and why their success rates are so low.

In contrast to DS, who experience tonic withdrawal symptoms and craving upon quitting because of the absence of nicotine in their system, and who may need medications (e.g., nicotine patch) that maintain steady-state nicotine levels, our study shows that ITS do not appear to experience such general or pervasive withdrawal effects when abstaining, and clearly do not need to maintain steady nicotine levels. However, a recently-proposed model suggests that ITS will experience intense cravings and 'need' to smoke after sufficient periods of abstinence. In contrast, we have proposed a stimulus control model that suggests that ITS do not experience craving at regular intervals, but only when they encounter situations associated with smoking, which may also cause relapse after ITS quit. Oral nicotine, which we have shown to acutely relieve cue-provoked situational cravings, is expected to lower the risk of relapse when used to cope with strong craving or temptation. (Conversely, "steady-state" medications such as patch, varenicline, or bupropion, seem less appropriate for ITS, given their intermittent smoking patterns.)

Despite growing prevalence, no treatment model for ITS has been validated. ITS (and light DS) have been systematically excluded from cessation trials, with the result that we know little about how to treat these populations. Shiffman reported that 2 mg nicotine lozenges worked well for 'light' smokers, but this was in a population of daily smokers of up to 15 cigarettes per day (near the average smoking rate). One study evaluated nicotine gum in 86 teen smokers (half active, half placebo), who might be thought of by some as analogous to ITS, and saw a trend towards better outcomes, but the study focused on dependent teens smoking 10 cigarettes or more daily. Compliance is also often reported as an issue in treating teens. A study of African-American adult (mostly daily) light smokers averaging 8 CPD found no significant effect of nicotine gum, but compliance with use of gum was low, and the dynamics of nicotine may be different in African-American populations. The one study of cessation in ITS tested counseling (not nicotine medications) in an unusual population: 20-year-old

military recruits not necessarily interested in quitting, and coming out of a 6-week period of enforced abstinence during basic training. In this context, the study saw high quit rates (much higher than seen in our population-based study), and no effect of counseling. Thus, no study has tested NRT among ITS, despite their growing prevalence and difficulty quitting.

The 2 mg nicotine gum is approved for all low-dependence smokers (i.e., those who report a time to first cigarette of >30 minutes), and light or intermittent smokers are not excluded. Nicotine gum has an extensive track record of safety, even when used concomitantly with smoking. In clinical practice, concurrent use typically consists of continued NRT use with occasional smoking during a quit attempt. Continuing NRT use while smoking does not appear to cause harm over and above the use of tobacco alone and, in fact, appears to prevent progression from lapse to relapse and thus help smokers return to abstinence.

Significance:

After reviewing the state of the science on ITS, a NIH panel emphasized the high priority of research on ITS' cessation and relapse patterns. Reviewers called for studies to evaluate treatments, including medications, to help ITS quit. This study answers those calls, as it would be the first study to assess medication to help ITS quit.

Developing a better understanding of ITS' smoking and of how to help them quit is essential to public health: it will not only assist a substantial fraction of hitherto-ignored smokers, but also strategically anticipate upcoming scientific, treatment, and public health needs that will arise if the proportion of ITS continues to grow. Further, assessing the effect of nicotine medications on ITS' quitting will shed light on the role of nicotine in ITS' smoking and difficulty quitting.

Studying smoking cessation among ITS is important for public health. Research on ITS' smoking cessation has practical and translational significance. ITS are at risk of death due to heart disease and lung cancer and are also at risk of progression to heavier smoking, which escalates the adverse health consequences. Accordingly, although their burden of disease is lower than that of DS, there is still a public health mandate to increase quitting in ITS. Intermittent smoking also disproportionately affects ethnic minorities, who have also been under-treated for smoking and related health consequences.

New models are needed to understand ITS' smoking. Conceptually, studying ITS can provide an important window into the dynamics of smoking cessation, relapse, and nicotine self-administration. The growing prevalence and persistence of ITS suggests that current models of smoking and cessation are incomplete, and need to be elaborated to account for ITS' smoking. Russell hypothesized that while most smokers smoke in order to maintain nicotine levels so as to avoid withdrawal (trough-maintainers), others smoke for the acute effects of nicotine in particular situations (peak-seekers). ITS better fit the profile of peak-seekers: they do not maintain nicotine levels, do not experience withdrawal when briefly abstaining voluntarily, and smoke in specific settings. Whether they are seeking nicotine could be clarified by assessing the effect of nicotine medications on abstinence. Furthermore, results from this study have the potential to improve the care of up to 25-33% of all current smokers, amounting to almost 10 million ITS in the US alone. ITS rarely receive help quitting smoking; indeed, no efficacious treatment for ITS has even been identified. Current DHHS guidelines stress the distinct lack of research in this area, and call for additional studies to assess treatments for ITS.

The combination of a randomized controlled trial with ecological momentary assessment (EMA) is an innovative and powerful research design. This approach efficiently captures data on the efficacy of NRT for smoking cessation among ITS, while also providing for micro-analysis of mechanisms for lapse and relapse, thereby addressing three major gaps in the understanding of ITS' smoking. First, we will determine the efficacy of oral NRT. Second, we will document, in real time, the experience of cessation, craving, and relapse in ITS, and how these are affected by nicotine medications. We will assess how closely temptation and relapse situations resemble baseline smoking situations, thus assessing the associational model of relapse. Third, we will determine the role of acute nicotine in acutely averting lapse and relapse. Since most usage of other addictive drugs is non-daily, a detailed analysis of relapse among ITS would be an invaluable contribution to our understanding of cessation of intermittent drug abuse, with potential applications beyond smoking.

Section 2 - Research Design and Methods

This study is a double-blind, randomized, placebo-controlled trial of acute nicotine replacement (low dose nicotine gum vs. placebo) in non-daily, intermittent smokers (ITS) who are motivated to quit smoking.

The screening procedures performed for the purpose of this research study:

Participants who expressed initial interest in learning more about the study will be provided with the study contact phone number. Potential participants may leave a message on our passcode-protected voice mail if they are unable to reach the study RA, who will then return their call. The study research assistant will read a brief description of the study, and then ask if they would like to participate in a brief confidential phone screening interview in order to determine whether they may be eligible. (Non-daily smokers who do not express interest in quitting will be read a brief description of another study being conducted by the Smoking Research Group, which examines the effect of very-low nicotine content cigarettes on smoking in non-daily smokers.)

Potential participants will also be provided with a study website address (www.smokingresearchgroup.com) in our advertisements. Potential participants will be able to access a short prescreen Qualtrics survey through this website. Going through this pre-screen potential participants will be able to identify as a daily or non-daily smoker, as well as answer a few additional questions about their smoking habits, which will help to determine whether they would be eligible for one of our studies (either this one or our other study for non-daily smokers).

Individuals who are willing to participate in the screening will then be asked a series of questions to ascertain their eligibility. Those who meet the eligibility criteria and wish to enroll will then be scheduled for an in-person appointment at the study site. Those participants who do not qualify will be asked if they would like for the study team to retain their answers and contact information, so that in the event that they may be eligible for future studies, we may contact them. Those participants answering yes will have that response documented, and may be contacted in the future. Callers who identify as daily smokers will be given contact information of other local studies more appropriately suited to their smoking patterns.

Screening information from individuals who do not enroll will also be retained in aggregated form without

identifying information, to be tabulated for the purpose of analyzing screening and recruitment statistics, and assessing potential volunteer bias. For subjects who volunteer, all information collected at screening will be retained at the study site for secure storage.

At the first in-person appointment, after the screening consent form is discussed and written consent to screen is obtained, a research assistant will review the phone screen questions with potential participants before officially enrolling the participant. The answers provided by the individual from the phone screen will be compared to the answers given in the in-person appointment to ensure consistency in self-report.

Additionally, prior to enrollment, a research assistant will issue to the individual a calendar based Timeline Follow-back which captures smoking patterns over the prior 30 days, and if it is found that the participant has smoked on 28 or more of the past 30 days, they will not be eligible to participate. Finally, all participants will be asked to give a breath sample which tests for level of carbon monoxide (CO) present in the breath. Those participants whose CO level is greater than 15 will not be enrolled in the study (as this indicates heavy smoking, and is not consistent with non-daily smoking.)

Detailed description of all research activities:

All procedures and study visits will be conducted by University of Pittsburgh staff research assistants, and will be held at the University of Pittsburgh Smoking Research Group laboratory (130 North Bellefield Ave., Suite 510, Pgh, PA 15213). All staff providing smoking cessation counseling will have completed the University of Massachusetts' nine-module online course, Basic Skills for Working with Smokers, as well as have attended either formal in-person Tobacco Treatment Specialist training offered by the University of Massachusetts, or in-person sessions at the University of Pittsburgh with a smoking cessation expert. All staff will be subject to supervision by PI.

The Study Flow Chart (below) details the overview, timing, and duration of study sessions and procedures, as well as a schematic of a day of Ecological Momentary Assessment (EMA) monitoring via electronic smart phone diary.

A brief overview of the study procedures are as follows (with more detailed visit-by-visit descriptions below):

Participants consenting to enroll in the study will be randomized to receive either nicotine gum or placebo gum, complete a baseline questionnaire assessment, and begin EMA monitoring while they prepare for a target quit date (TQD) 2 weeks later. Participants begin study medication on the 3rd visit, the TQD (at the start of week 2 of the study) and continue using it for 8 weeks (to study week 10). Participants will attend 6 in-person, one-on-one brief behavioral support sessions. Two weeks prior to the TQD and continuing for 6 weeks afterwards, participants will carry a smart phone programmed to collect real-life data in real time on their smoking (ad lib smoking, lapses) and craving (temptations), and the situations in which these events occur (e.g., when others are smoking). Participants will also report on what (if any) occasions they are using other nicotine-containing products, such as e-cigarettes or smokeless tobacco. During the 2 week pre-quit period, participants will record all cigarettes smoked, all temptations to smoke, and any use of other nicotine-containing products. They will also be prompted at random to assess their state and behavior when they are not smoking (see attached schematic of a typical EMA day). Beginning with their first day of their quit attempt, and for 6 weeks after, participants will record all temptations to smoke and any lapses they have, as well as their use of study medication and any other nicotine-containing products, and they will continue to complete randomly-scheduled assessments. Biochemical validation of smoking status will also be undertaken. The primary efficacy outcome is

continuous abstinence at 6 months (defined by biochemically-validated abstinence at 12 and 24 weeks, combined with self-reported abstinence on the TQD and all subsequent study visits).

Medicinal nicotine gum will be sent to the Smoking Research Group laboratory in care of a designated staff member. The shipment will be inspected for damage and its contents reconciled with the accompanying Shipping Notice. The inventory will be logged using a standard tracking form. Packing slips will be filed in a secure location. Any damage or discrepancies in the shipment will be reported promptly for corrective action. The gum will be stored in a locked, secure area with limited access. Manufacturer recommendations regarding storage conditions (i.e., temperature) will be followed.

Study Flow Chart:

Study Visits: Timeline, Procedures and Duration

	Baseline EMA		Quit Attempt / EMA Monitoring								Outcome	6 mo f/up	
Study Visit	1	2	3	4	5		6		7		8	9	
Duration of Visit (min)	120 min	60 min	60 min	60 min	60 min		60 min		60 min		30 min	30 min	
Baseline assessment	■	■	■										
Timeline Followback	■		■	■	■		■		■				
Biochemical validation (urine)	■	■									■	■	
Biochemical validation (CO)	■	■	■	■	■		■		■		■	■	
Weight (and Height only at visit 1)	■	■	■	■	■		■		■		■	■	
Counseling		■	■	■	■		■		■				
EMA monitoring	■	■	■	■	■	■	■	■	■				
Study medication (NRT or placebo)			■	■	■	■	■	■	■	■	●		
Exit Interview												■	
Week (in relation to quit)	-2	-1	0 (TQD)	1	2	3	4	5	6	7	8	12	24
Study Week	0	1	2	3	4	5	6	7	8	9	10	14	26
Payment	\$10	\$15	\$20	\$20	\$25		\$25		\$75		\$75	\$75	

● participants return unused product

● participants return unused product

A full description of visit-by-visit procedures follows below:

Visit 1:

-Screening Consent: Participants will be told about screening procedures and asked for consent for screening procedures.

- Breath CO testing: Participants will be asked to provide a breath sample, in order to measure the level of carbon monoxide (CO) present in their bloodstream. Exhaled CO will be measured with a digital carbon monoxide monitor (Vitalograph, Inc., Lenexa, KS). Breath sampling will take approximately 1 minute. Participants will be instructed to take three deep cleansing breaths, take a deep breath and hold it for 10-15 seconds, and then exhale completely into the collection tube. Breath samples at Visits 1 and 2 will be used to establish a baseline level of CO present under normal smoking conditions. Breath samples at all subsequent visits (i.e., 3 through 9) will be used to verify participants' abstinence from (or relapse to) smoking.

- Time line follow back (TLFB) of smoking behavior: Participants will complete a calendar-based TLFB report of their smoking behavior, which will cover the previous 30 days.

- **Consent:** During the first session, participants will be described study procedures in detail and asked to provide written informed consent.

- **Urine cotinine testing:** Because breath CO sampling alone may not be sufficient to verify presence or absence of smoking, given that ITS' baseline smoking is by definition light and intermittent (and thus, may not be adequately captured by the relatively insensitive measure of expired CO), participants will also be asked to provide a urine sample at four visits (visits 1, visit 2, visit 8 and visit 9). Urine samples will be analyzed for levels of cotinine (the primary metabolite of nicotine, and a biological marker of nicotine consumption) metabolized and excreted in participants' urine at each visit. Participants will be provided with sterilized containers for urine collection. The pre-quit samples collected at visit 1 and visit 2 will serve to establish a baseline, pre-quit-attempt level of cotinine excreted, under normal smoking conditions. Collections at Visits 8 and 9 (12- and 24-weeks post quit-attempt, respectively) will be analyzed to verify participants' claimed abstinence from smoking, if applicable.

- **Height and weight measurement:** A measurement of participants' height and weight will be obtained at Visit 1 and measurements of weight only will be taken at each subsequent visit. These will be measured using a professional-grade medical scale. The measurements at Visits 1 and 2 will be averaged together in order to establish participants' baseline, pre-quit body-mass index (BMI), and this will be compared to subsequent, post-quit measurements.

- **Baseline questionnaire assessments:** Participants will be asked to complete the following panel of questionnaire and interview assessments. Demographics. Demographic information (e.g., age, gender, education, income, occupation, ethnicity, marital status). Current smoking and smoking history. We will collect smoking information (e.g., age at initiation, cigarettes per day, years smoked, past quit efforts, difficulty quitting, etc.) Dependence. Subjects will complete multiple measures of nicotine dependence, including the Nicotine Dependence Syndrome Scale, which yields 5 factors of dependence, and differentiates among aspects of dependence, characterizing the "dependence profile" of the samples. We have shown that these measures are sensitive to variations in dependence among ITS. We will also administer the Fagerström Test for Nicotine Dependence and the Wisconsin Inventory of Smoking Dependence Motives-Brief. Motivation for quitting. We will assess participants' qualitative reasons for quitting (i.e., health, expense, social pressure, etc.). Self-efficacy. We will use our scale of self-efficacy, which captures both an overall efficacy measure, and differentiation by situational cues, allowing situation-specific efficacy to be related to temptation and lapse patterns. Lifetime smoking and quitting history. We will assess subjects' smoking history; e.g., how ITS have smoked in the past, and the trajectory of smoking that brought them to their current smoking status. The interviews will capture past quitting efforts and their outcomes. In prior research, we adapted cognitive interviewing methods to gather data about various phases in each smoker's smoking career. This has been used to identify native vs. converted chippers and ITS, and has been widely adapted and validated. Smoking in the social network. We will use the relevant items from the BRFSS and other national surveys to assess smoking behavior in subjects' social network, including ITS' smoking, and attitudes towards smoking. Alcohol quantity/frequency. We will collect drinking data through administration of questions adapted from the Alcohol Craving Questionnaire, and from the AUDIT-C, which has high sensitivity for problem drinking. Family history of smoking. Participants will report on biological parents' smoking history. We found that family history differentiated chippers and regular smokers. Psychopathology. We will administer the Kessler 6 (K6), a widely validated measure of general depression and/or anxiety. Smoker self-identity. We will include a 7-item scale to assess the degree to which participants identify with being a "smoker." Perceived health risks of smoking. We will ask participants to report perceived smoking related health risks, both comparatively and absolutely. We will administer the 6-item Life Orientation Test –Revised (LOT-R) and the 8-item Optimistic Bias scale. ITS' beliefs that they are vulnerable to

health effects from smoking may be a key motivational variable. The baseline assessment is expected to take ~1.5 hours to complete, and will be administered over the course of visits 1 and 2.

- **EMA Monitoring Training:** Participants will be trained to use an electronic diary (ED; programmed on a smartphone-like device) to monitor their smoking behavior, craving, and use of study medication. The use of a palmtop computer an essential aspect of the method (see Shiffman et al., 2000). The ED interface is very simple and clear, so that no computer or PDA/smartphone familiarity is assumed or required. ED protocols have been executed successfully by computer naive, poorly educated, and very elderly subjects.

Training will take approximately 45 minutes. Participants will be instructed in how to make entries in the ED, as well as how to contact study staff with questions or should technical problems occur.

ITS will be asked to record all episodes of smoking. Smoking occasions (considered to be “slips” after participants’ Quit Date) are sampled for assessment such that each individual is expected to receive no more than approximately 5 assessments per day (though note that it is expected that most participants will not smoke to that extent, and thus will completed far less assessments). Participants are additionally assessed when they report a temptation, defined as a strong episode of craving during which they came close to smoking. ED will additionally “beep” subjects at approximately 4 randomly-selected times each day, administering an assessment of participants’ current mood, craving, and activity.

At the end of the session, participants will be asked to set a tentative target quit date (TQD) on which they will agree to attempt to quit smoking. This date will be approximately two weeks after the date of their first visit.

Visit 2:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1).

- **Urine cotinine testing:** Participants will be asked to provide a urine sample, as described in detail above (see Visit 1).

- **Weight measurement:** A measurement of participants’ weight will be obtained using a professional-grade medical scale.

- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.

- **Cessation Counseling:** Participants will be provided with information regarding short- and long-term health risks of smoking – including those incurred at even low (i.e., non-daily) levels of cigarette consumption, the toxic ingredients found in cigarettes and tobacco, and the detrimental effects of second-hand smoke on those exposed to it. Participants will be reminded of the date on which they committed to making an attempt to quit smoking, which will also coincide with their next study visit (i.e., Visit 3), and will be permitted to adjust the date if need be. Staff research assistants certified in cessation counseling techniques (as described previously) will also advise participants on how to prepare for their quit date (e.g., discarding cigarettes and smoking-related paraphernalia, notifying family, friends, and coworkers of their quit date and asking for support, etc.) and will ask participants to articulate and thereby reinforce their personal reasons for wanting to quit smoking. Finally,

research assistants will review strategies for dealing with issues that may arise for each individual on that first day of abstinence.

- **Baseline questionnaire assessments:** Participants will be asked to finish the panel of baseline questionnaire assessments, begun (and described) in the previous visit (i.e., in Visit 1)

- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant.

Visit 3 (Quit Date):

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.

- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.

- **Cessation Counseling:** Participants will take part in behavioral cessation counseling, whereby research staff will ask participants to describe their initial thoughts on quitting, explain nicotine withdrawal (if relevant), help participants to identify any situations which may pose a challenge to their ability to successfully abstain (or which may arise in the future), and develop and document personalized strategies with each participant, designed to help them to prepare for how to handle these challenges.

- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant.

- **Study Medication:** Participants will be dispensed a two-week supply of study medication (previously randomized to be either active or placebo nicotine replacement gum) and the study RA will demonstrate to participants how to properly use the gum, in accordance with the FDA-approved instructions (i.e., chewing only for 1-2 times and then "parking" the gum between the tooth row and cheek, in order to allow the medicine to be absorbed by the cheek, as opposed to being swallowed, which would inactivate the medicine). Participants will be asked to try a piece of gum in front of the study RA. Participants will be advised on how to contact study staff at any time, in the event that have any additional questions or believe that they experience any adverse effects. The quantity of gum provided will be equal to the number of self-reported cigarettes per day, which has been shown to average 4-5 in this population.

Visit 4:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.
- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.
- **Cessation Counseling:** Participants will also take part in behavioral cessation counseling, whereby research staff will identify, document, and review with participants which cessation strategies have they employed, and whether each has helped them to successfully abstain from smoking since their quit date. Continued use of successful strategies will be encouraged. If applicable, any smoking lapses (i.e., occasions on which participants may have smoked) that have occurred in the interval since their previous study visit will be identified and documented, and research assistants will engage participants in formulating alternate strategies designed to help them to remain abstinent in similar situations in the future.
- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant.
- **Study Medication:** Participants will be dispensed an additional week's supply of study medication (previously randomized to be either active or placebo nicotine replacement gum) and the study RA will record participants experiences in using the gum, such as perceived effectiveness in aiding quit attempt, any adverse or unexpected effects, etc.. Participants will be reminded how to contact study staff at any time, in the event that have any additional questions or believe that they experience any adverse effects. The quantity of gum provided will be equal to the number of self-reported cigarettes per day, which has been shown to average 4-5 in this population.

Visit 5:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)
- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.
- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.
- **Cessation Counseling:** Participants will also take part in behavioral cessation counseling, whereby research staff will identify, document, and review with participants which cessation strategies have they employed, and whether each has helped them to successfully abstain from smoking since their quit date. Continued use of successful strategies will be encouraged. If applicable, any smoking lapses (i.e., occasions on which participants may have smoked) that have occurred in the interval since their previous study visit will be identified and documented, and research assistants will engage participants in formulating alternate strategies designed to help them to remain abstinent in similar situations in the future.

- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant.

- **Study Medication:** Participants will be dispensed an additional week's supply of study medication (previously randomized to be either active or placebo nicotine replacement gum) and the study RA will record participants experiences in using the gum, such as perceived effectiveness in aiding quit attempt, any adverse or unexpected effects, etc.. Participants will be reminded how to contact study staff at any time, in the event that have any additional questions or believe that they experience any adverse effects. The quantity of gum provided will be equal to the number of self-reported cigarettes per day, which has been shown to average 4-5 in this population.

Visit 6:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.

- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.

- **Cessation Counseling:** Participants will also take part in behavioral cessation counseling, whereby research staff will identify, document, and review with participants which cessation strategies have they employed, and whether each has helped them to successfully abstain from smoking since their quit date. Continued use of successful strategies will be encouraged. If applicable, any smoking lapses (i.e., occasions on which participants may have smoked) that have occurred in the interval since their previous study visit will be identified and documented, and research assistants will engage participants in formulating alternate strategies designed to help them to remain abstinent in similar situations in the future.

- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant.

- **Study Medication:** Participants will be dispensed an additional week's supply of study medication (previously randomized to be either active or placebo nicotine replacement gum) and the study RA will record participants experiences in using the gum, such as perceived effectiveness in aiding quit attempt, any adverse or unexpected effects, etc.. Participants will be reminded how to contact study staff at any time, in the event that have any additional questions or believe that they experience any adverse effects. The quantity of gum provided will be equal to the number of self-reported cigarettes per day, which has been shown to average 4-5 in this population.

Visit 7:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.

- **Time line follow back (TLFB) of smoking behavior:** Participants will also complete the TLFB (calendar of daily smoking behavior), retrospectively covering the time period elapsed since their previous visit to the lab.

- **Cessation Counseling:** Participants will also take part in behavioral cessation counseling, whereby research staff will identify, document, and review with participants which cessation strategies have they employed, and whether each has helped them to successfully abstain from smoking since their quit date. Continued use of successful strategies will be encouraged. If applicable, any smoking lapses (i.e., occasions on which participants may have smoked) that have occurred in the interval since their previous study visit will be identified and documented, and research assistants will engage participants in formulating alternate strategies designed to help them to remain abstinent in similar situations in the future.

- **EMA monitoring check-in:** Project staff will review with participants the degree to which they met study compliance standards. Any questions or issues that arise with regard to use of the ED will be addressed with the participant. The participant will also be asked to return to the study staff the ED at this visit.

- **Study Medication:** Participants will be dispensed an additional week's supply of study medication (previously randomized to be either active or placebo nicotine replacement gum) and the study RA will record participants experiences in using the gum, such as perceived effectiveness in aiding quit attempt, any adverse or unexpected effects, etc.. Participants will be reminded how to contact study staff at any time, in the event that have any additional questions or believe that they experience any adverse effects. The quantity of gum provided will be equal to the number of self-reported cigarettes per day, which has been shown to average 4-5 in this population.

Visit 8:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.

- **Urine cotinine testing:** Using procedures described previously (see Visit 2), participants who report continued abstinence at Visit 8 (12 weeks post-quit) will be asked to provide a urine specimen, for testing for the nicotine metabolite cotinine. This will serve to verify their self-reported abstinence.

- **Study Medication:** Participants will be asked to return to the study staff any unused portion of their study medication at this visit, and no additional will be dispensed.

Visit 9:

- **Breath CO testing:** Participants will be asked to provide a breath measurement of exhaled CO, as described in detail above (see Visit 1)

- **Weight measurement:** A measurement of participants' weight will be obtained using a professional-grade medical scale.

- **Urine cotinine testing:** Using procedures described previously (see Visit 2), participants who report continued abstinence since Visit 8 (12 weeks post-quit) will be asked to provide a urine specimen, for testing for the nicotine metabolite cotinine. This will serve to verify their self-reported abstinence.

Follow- up Procedures:

We will send a feedback form to participants who drop out or are discontinued to potentially help with participant retention in the future. The form will include questions such as what made it difficult to participate in the study and ways to improve the study. The form should take approximately 5-10 minutes to complete.

We will give an exit interview questionnaire to participants. The exit interview questionnaire will be administered when a participant has completed the study or has ended participation in the study and takes about 10- 15 minutes. The exit interview questionnaire is a survey designed to ask participants information about their experience with the study, their current smoking behaviors, and if they knew what condition they were in.

The total duration of the subject's participation in this research study across all visits, including follow-up surveillance:

26 weeks

Banking of biological specimens:

Urine cotinine testing. Participants will also be asked to provide a urine sample at lab visits 1, 2, 8, and 9 so that the level of excreted cotinine (the primary metabolite of nicotine, and a biological marker of nicotine consumption) can be measured during regular smoking conditions (visit 2), and at post-quit visits 8 and 9, to verify abstinence, if claimed. Participants will be provided with sterilized containers for urine collection. Urine samples will be stored once analyzed, so that the samples for subjects claiming abstinence, whose cotinine level is < 25 ng/ml can be sent out for analysis of the tobacco-specific nitrosamine metabolite 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol (NNAL), which has a long half-life (10-16 days), and is thus the most sensitive to use in this population.

The samples will be under the control of the principal investigator of this project. All personal identifiers (i.e., name, social security number, birth date) will be removed and replaced with a specific code number. The information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location. Samples will be kept indefinitely.

The main outcome variables that will be evaluated:

Aim 1: Test whether nicotine gum can help ITS quit smoking. H1: ITS randomized to oral NRT will have higher rates of 6 month abstinence compared to ITS using placebo.

Aim 2: Use EMA methods to capture quit and relapse process in ITS.

Sub-aim 1: Test whether ITS suffer increasing craving and withdrawal-like distress after prolonged and variable periods of abstinence. H2-1: ITS will suffer resurgence of craving and withdrawal after an individual-specific interval of abstinence.

Sub-aim 2: Test whether ITS' temptations and lapses occur specifically in situations previously associated with their individual smoking patterns, as implied by a stimulus control theory of ITS' smoking and relapse. H2-2: ITS' temptations and lapses will be predictable based on their baseline smoking patterns.

Section 3 - Human Subjects

Inclusion Criteria:

- Must be 18+ years old
- Must have smoked for at least 3 years
- Must have been non-daily smokers for one year ($< \text{or} = 27$ days/month); and smoke at least weekly.
- Must report an intention to quit smoking within the next month and a desire to receive behavioral and medication treatment.
- Must be willing and able to come to the University of Pittsburgh's Smoking Research Group lab for 8 visits over a 14-week period, as well as a ninth and final visit 6 months after their quit date, and to monitor behavior via an electronic diary for 8 weeks.
- Must be able to read and write English, since most of the study questionnaires are currently validated only for English-speaking populations.

Exclusion Criteria:

- Regular use of any form of tobacco other than cigarettes
- Recent or severe mental illness (uncontrolled severe depression or mood symptoms, active hallucinations, or hospitalization in the past month for a psychiatric condition)
- Night and/or 'swing' shift work (which complicates EMA schedules)
- Known plans to relocate or move from the Pittsburgh area within the coming 6 months
- Received cessation treatment (including cessation counseling, NRT, bupropion, or varenicline) in past 2 months
- Contraindication to NRT
- For women, current pregnancy or breastfeeding or plan to become pregnant during the next 2 months
- Multiple members of the same household cannot participate
- Participation in more than 3 research studies in the past 6 months
- Participation in a smoking study in the past 6 months
- Participation in a study which involved medication within the last month
- Prior to enrollment at first session, reporting smoking 28 or more days of the past 30, or registering a CO reading of 15 or above (as this indicates heavy smoking, and is not consistent with non-daily smoking)

Section 4 - Subject Recruitment and Informed Consent Procedures

Recruitment methods, including identifying and initiating contact with participants:

We will employ methods our group has successfully used in past studies, including advertisements through the University of Pittsburgh Medical Center (UPMC) clinical system, in local periodicals and social networking sites (e.g. Facebook, Craigslist, Twitter, YouTube), on television, local radio stations, mass transportation, and via free public service announcements earmarked for research; the patient registry of the Pitt Clinical Translational Science Institute; and word of mouth.

We will also make use of the clinical Tobacco Treatment Service at UPMC Presbyterian and Montefiore, which targets approximately 8600 unique smokers admitted annually. The TTS proactively approaches smokers and counsels them to quit. Following the clinical encounter, individuals who express interest in participating in ongoing research studies involving smoking and who give their permission to be contacted will be referred to the study RA to be contacted by phone and screened for eligibility after hospital discharge.

We will also use the Text for Info system on our advertisements, a SOSI (secure online subject interaction) from UPMC department of psychiatry's academic computing. This allows potential participants to text a number with a code word which will reply to them via text with more information about our study.

Our website www.smokingresearchgroup.com will be included on our advertisements. It contains basic information about the study and the short web screen interested visitors can fill out.

The process that is employed to ensure the subjects are fully informed about this research study:

A study RA will review the Informed Consent document, including a description of the study, procedures, risks and benefits, and provide an opportunity to ask questions about the study. The participant will then be asked to provide written consent before proceeding with enrollment and randomization. Information about the study will be provided over the phone before participants attend the in-person consent signing, thus providing participants with ample time to consider involvement in the research.

Section 5 – Data and Safety Monitoring

We will protect against breaches of confidentiality on phone lines by not disclosing information about participants' participation in the study to others who share a phone line with participants. We will leave the minimum amount of information necessary on participant answering machines with permission from the participant. Participant data (participant questionnaires, progress notes from smoking cessation counselors) will be collected using written or printed records or password-protected computers. These will be stored in a locked filing cabinet in a locked room. Electronic participant tracking data will be stored on a secure server within the University of Pittsburgh firewalls, which are password protected, and anti-virus software enabled computer systems.

Only study staff will have access to the study data on secured Shared File Areas. Participants will be identified on study forms and in the database by a unique participant ID number only. Participant names and contact information will be stored separately from the study data.

Participants will provide urine samples which will be shipped to a contracted laboratory for analysis. These samples will be deidentified and will contain only a unique ID number.

We will protect against risks of psychological discomfort by using smoking counselors who are trained in tobacco cessation and treatment. In addition, participants will be told that they can refuse to answer any questions or terminate contact with counselors at any time.

NRT gum is FDA approved for use in smoking cessation, is available “over-the-counter”, and is generally considered safe for use. In order to protect against risk from NRT, these steps will be taken:

- (1) Potential participants will be screened for contraindications to NRT, and excluded from the study.
- (2) Study subjects will be given instructions about gum use on an “as needed basis”, and be educated about any potential adverse effects by the study staff, including how to handle any potential adverse effects (i.e., to reduce or stop using the gum if symptoms occur and to call the study staff in case of any problems).
- (3) Low dose nicotine gum (NRT) is being provided to subjects in the intervention arm only, however the intervention is blinded. All subjects will be asked about any problems using the gum during study sessions occurring regularly during study weeks 3 - 10. Study staff will report any unexpected or questionable reports of adverse effects to Dr. Primack, Tindle and/or Dr. Shiffman. Any reports of serious adverse events will be reported immediately to Dr. Primack, Tindle and/or Dr. Shiffman who will contact the participant and the IRB according to the timelines and guidelines for the University of Pittsburgh.

Since NRT gum is not established therapy for smoking cessation among non-daily smokers, giving participants placebo gum does not constitute withholding care. All participants will be receive established treatment (behavioral counseling sessions) for help with quitting smoking, regardless of whether also receiving “active” (NRT) gum or “inactive” (placebo) gum.

Data and safety monitoring plan:

The PI has responsibility for the oversight of individuals enrolled in the study.

An independent Data Safety Monitoring Board (DSMB) will be commissioned for this study and will monitor the progress of the study, data quality, and ensure that the safety of subjects is not compromised. The DSMB will consist of 3 members, all of whom are experienced tobacco investigators, and all of whom have agreed to participate: Jonathan Foulds (psychologist, Penn State Medical School); John Hughes (physician/psychiatrist, University of Vermont); and Peter Callas (statistician, University of Vermont). The DSMB will meet up to twice annually beginning in year 2 of the study.

In addition, the core study team (i.e., Dr. Primack, Tindle, Dr. Shiffman, Project Coordinator, and Research Assistants) will meet at least monthly during recruitment to review AEs, SAEs, UAPs and subject withdrawals, and to monitor study progress and recruitment activities.

Study staff will immediately notify Drs. Primack, Tindle, and Shiffman of any UAPs or SAEs reported by subjects. Drs. Primack, Tindle, and Shiffman will review for risk and study-relatedness (including any changes to the risk-benefit dynamic). UAPs and SAEs will be reported to the IRB according to University of Pittsburgh IRB Guidelines.

A summary of DSMB meetings, as well as monthly internal project monitoring meetings, will be provided to the IRB at time of annual review.

The procedures utilized to protect subject confidentiality, following the required data retention period:

All records pertaining to subjects' involvement in this study will be kept in secured long-term storage for a minimum of seven years after completion of the study. After this period, all files containing identifying information will be destroyed, including that which contain links to participant ID codes. Paper documentation will be cross-cut shredded, and electronic files wiped from hard disk, according to University of Pittsburgh IT guidelines.